IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Randolph J. Noelle et al.

Application No.: 09/164,568 Confirmation No.: 6823

Filed: October 1, 1998 Art Unit: 1644

For: METHODS FOR INDUCING ANTIGEN-SPECIFIC T CELL TOLERANCE Examiner: P. Gambel

APPEAL BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This appellant's Appeal Brief under 37 C.F.R. § 41.37 is submitted in support of their appeal from the Panel Decision from Pre-Appeal Brief Review dated January 25, 2007 in the above-identified patent application.

In accordance with the Pre-Appeal Brief Conference Pilot Program, "[t]he time period for filing an appeal brief will be reset to be one month from mailing of the decision on the request, or the balance of the two-month period running from the receipt of the notice of appeal, whichever is greater." Because the Panel Decision was mailed January 25, 2007, and the Notice of Appeal was filed December 13, 2006, Applicants submit that they are entitled to one month from the mail date of the Panel Decision to file the present Appeal Brief with no extension fees (*i.e.*, February 25, 2007). Therefore, Appellants submit that this Appeal Brief is timely filed. However, the Commissioner is hereby authorized to charge any unpaid fees deemed required in connection with this Appeal Brief, or to credit any overpayment, to Deposit Account No. 04-0100.

I. Real party in interest

The real party in interest is Dartmouth College, the assignee of this application by virtue of the assignments recorded on August 26, 1994 at Reel 7117, Frame 0046, September 9, 1994 at Reel 7112, Frame 0383, and September 30, 1994 at Reel 7150, Frame 0874.

II. Related appeals and interferences

There are no related applications under appeal or as the subject of an interference that are related to, or would directly affect the pending appeal.

III. Status of claims

Claims 82-94 are pending, rejected and are being appealed. Claims 1-81 have been cancelled. Claims 1-94 are attached hereto in the "Claims Appendix."

IV. Status of amendments

The final Office Action was transmitted on June 14, 2006. A Response pursuant to 37 C.F.R. 1.116 was submitted to the United States Patent and Trademark Office on August 9, 2006. No claim amendments were made in that Response. In an Advisory Action mailed August 31, 2006, the Examiner stated that the Applicants' arguments did not put the application in condition for allowance.

On December 13, 2006 a Pre-Appeal Brief Request for Review was submitted in accordance with the Pre-Appeal Brief Conference Program together with a Notice of Appeal. A Notice of Panel Decision from Pre-Appeal Brief Review was mailed on January 25, 2006 wherein the Panel: (1) determined that the application remains under appeal because there is at least one actual issue for appeal; and (2) maintained the rejection of claims 82-94.

V. Summary of claimed subject matter

The currently claimed invention is a method of reducing antigen-specific T cell responsiveness *in vivo* comprising the administration of (a) an antigen-presenting cell (APC) that presents an autoantigen to an activated T cell expressing mouse or human gp39 **and** (b) an anti-gp39 antibody which binds to mouse or human gp39 on the activated T cell, wherein the anti-gp39 antibody is administered prior to, concurrent with, or subsequent to administration of the APC in an amount effective to reduce T cell responsiveness to the antigen-presenting cell (claims 82-94).

This invention is based, at least in part, on the discovery that cell-surface molecules which mediate contact-dependent helper effector functions also play a critical role in the response of T cells to antigens. The inventors determined that the APC which presents the antigen to the T cell requires an interaction between a gp39 ligand on the cell (*e.g.*, CD40), and the gp39 on the T cell in order to provide signals necessary for activation of the T cell. Inhibition of the interaction between the gp39 ligand and the gp39 prevents T cell activation by the presented antigen, and induces antigen-specific T cell tolerance, *i.e.*, reduces T cell responsiveness (claims 82-94; specification, page 3, ll. 5-14; page 6, ll. 10-12; page 9, ll. 22-25.). Interference with activation of the T cell via gp39 may prevent the induction of co-stimulatory molecules on the APC so that the APC delivers an antigenic signal in the absence of the co-stimulatory signal, thus inducing tolerance (specification, page 9, ll. 29-34).

This inhibition is achieved by administering an APC with a gp39 antagonist. A gp39 antagonist is defined as a molecule which interferes with the interaction of gp39 on a T cell with a gp39 ligand on the APC (specification, page 6, ll.29-33). The gp39 antagonist can be an anti-gp39 antibody (claims 92-94; specification, page 6, ll. 33-35).

An antigen presenting cells is one which can present antigen to T cells and includes B lymphocytes, "professional" antigen presenting cells such as monocytes, dendritic cells, and Langerhan cells, and other cells such as keratinocytes, endothelial cells, astrocytes, fibroblasts, and oligodendrocytes (claims 83-91; specification, page 9, l. 34-page 10, l. 1).

The method of the present invention can be applied to induce T cell tolerance to a variety of antigens, including autoantigens involved in autoimmune diseases or disorders associated with abnormal immune responses (specification, page 13. l. 37-page 14, l. 4).

VI. Ground of rejection to be reviewed on appeal

The sole ground for rejection on appeal is whether claims 82-94 are unpatentable under 35 U.S.C. § 103(a) as obvious over Lederman *et al.* (U.S. Patent No. 6,403,091 ("Lederman"), in view of Beschorner *et al.* (U.S. Patent No. 5,597,563) ("Beschorner"), Cobbold *et al.* (U.S. Patent No. 5,590,933) ("Cobbold"), and Eynon *et al., J. Exp. Med.* 175:131-138 (1992) ("Eynon").

VII. Argument

A. Rejection of Claims 82-94 under 35 U.S.C. § 103, as obvious over Lederman in view of Beschorner, Cobbold and Eynon

Claims 82-94

The Examiner improperly rejects claims 82-94 as obvious over the combination of Lederman with any of the other cited references. The Examiner has not established a prima facie case of obviousness as set forth by MPEP § 2143 which requires that three basic criteria be met:

(1) the references taken alone or in combination must teach or suggest all of the claimed limitations:

(2) there must be some suggestion and/or motivation in the references or in the general knowledge of one having ordinary skill in the art to modify or combine reference teachings;

and

(3) there must be a reasonable expectation of success.

As shown below, the Examiner has failed to establish any one of the basic criteria, let alone all three.

(1) The Examiner has failed to prove that the cited references either alone or in combination teach all of the limitations of claims 82-94

The current claims call for a method that comprises the administration of (a) an antigen-presenting cell (APC) that presents an autoantigen to an activated T cell expressing mouse or human gp39 **and** (b) an anti-gp39 antibody that binds to mouse or human gp39 on the activated T cell. The prior art cited by the Examiner does not disclose or suggest, either alone or in combination, both steps of the claimed method for reducing antigen-specific T cell responsiveness.

Step (a) – administration of an antigen presenting cell that presents an autoantigen to an activated T cell expressing mouse or human gp39

The first step, administration of an APC, is not taught or suggested by the primary reference, Lederman. The Examiner has conceded this fact: Lederman is completely silent as to the administration of APCs to an activated T cell together with an anti-gp39 antibody. See Office Action dated October 22, 2002, page 3. Moreover, Lederman does not provide any functional data using activated T cells.

The Examiner relies upon the secondary references, Beschorner, Cobbold and Eynon, to provide the missing limitation of the use of APCs for the induction of tolerance. However, as shown below, these references do not cure Lederman's defects and are distinguishable from the presently claimed invention.

The Examiner contends that Beschorner discloses the use of APCs to induce tolerance to autoantigens or self antigens in the treatment of autoimmune disease by the co-administration of APCs and an immunosuppressant, and that this disclosure, combined with Lederman, renders the present claims obvious. This contention is simply incorrect.

Beschorner teaches the administration of APCs in an environment, *i.e.*, the blood, ***devoid of mature, activated T cells***, *i.e.*, subsequent to the use of a general immunosuppressive agent (Beschorner, col. 5, ll. 5-8; col. 8, ll. 1-13). This is disclosed by Beschorner in the discussion regarding the measurement of the effects of the immunosuppressant by evaluating the increased levels of cortical thymocytes, *i.e.*, *immature T cells*, outside the thymus, in the blood. Such immature thymocytes (immature T cells) are not ordinarily present in the peripheral blood, because they develop into mature T cells, either CD4+ or CD8+ cells, in the thymus. In Beschorner, administration of the immunosuppressant prevents development of the immature thymocytes into mature T cells. See Beschorner, col. 5, ll. 21-39.

Not only are the T cells in Beschorner not mature, they cannot become activated. In order for T cells to become activated in the thymus, contact with an APC harboring an antigen is required. The immunosuppressant used in Beschorner depletes the thymus of endogenous APCs (prior to the administration of exogenous APCs) (Beschorner, col. 5, ll.12-17; col. 7, ll. 3-6; col. 8, ll. 32-34). Thus, any already mature T cells present in the thymus at the time of the administration of the immunosuppressant, cannot become activated.

Beschorner does not suggest or disclose the missing limitation of Lederman: administration of an APC to *an activated T cell*. The administration of the immunosuppressant in Beschorner depletes the thymus of both activated, mature T cells, and any T cell precursors, as the former cannot become activated and the latter are prematurely released from the thymus. The Examiner never addresses this missing limitation in his office actions, stating only that Beschorner teaches "the use of antigen containing antigen-presenting cells for inducing tolerance to autoantigens or self antigens in the treatment of autoimmune diseases by administering the said antigen containing antigen presenting cells and an immunosuppressive." See, *e.g.*, Office Action dated June 14, 2006, page 4. The present invention depends upon the APC presenting antigen to an activated T cell. This important claim limitation is not disclosed or suggested in the teachings of Beschorner.

The Examiner also relies upon Cobbold to teach the limitation missing from Lederman, *i.e.,* administering APCs. Again, this reliance is misplaced. Cobbold is ***completely silent*** as to the administration of APCs, much less its co-administration with an anti-gp39 antibody. Cobbold discloses only the co-administration of anti-CD4 and anti-CD8 monoclonal antibodies to induce T cell tolerance and prevent skin graft rejections (Cobbold, abstract, col. 3, ll. 15-15 and ll. 39-47). Cobbold explicitly states that the skin graft or the antigen itself provides the source of antigen, not exogenously administered APCs (Cobbold, col. 3, ll. 56-61; col. 15, ll. 38-48).

Cobbold discloses neither of the limitations presently claimed (administration of an APC and administration of an anti-gp39 antibody) and thus, either alone, or in combination with Lederman, does not teach or suggest every limitation of the claimed invention.

The third reference relied upon by the Examiner to provide the missing limitation of administering APCs is Eynon. Like Beschorner and Cobbold, there is no hint of this limitation in Eynon. Instead, Eynon discloses presentation of antigen by a B cell to a "small resting T cell" and "unprimed T cells"- not to activated T cells expressing mouse or human gp39 (Eynon, p. 131, col. 2, ¶ 1; p. 135, col. 2, ¶ 1). Again, the Examiner never addresses this missing limitation stating only that Eynon discloses "both antigen-specific B cells and small resting B cells can serve as antigen presenting cells in tolerizing regimens." See Office Action dated June 14, 2006, page 3.

Additionally, Eynon does not even disclose administering an APC to induce tolerance, but instead relies upon a population of endogenous APCs (small resting B cells) to process the antigen and present it to un-activated T cells (Eynon, p. 131, col. 2, ¶ 1; p. 135, col. 2, ¶ 1). Moreover, the tolerance induced by the method was transient (Eynon, p. 136, col. 1, ¶ 2). This transient tolerance would be useless for the indications of the present invention.

The only administration of an APC disclosed by Eynon is in the context of testing whether T cell tolerance was induced by her method, which involves taking T cells out of a mouse that had been administered the antigen and putting such T cells in SCID mice along with normal B

cells to determine if the T cells could activate the B cells. However, this is a method of evaluating tolerance, not inducing it.

Thus, none of the cited references, Lederman, Beschorner, Cobbold, or Eynon, teach or suggest the first step of the claimed method: administration of an APC that presents an autoantigen to an activated T cell expressing mouse or human gp39. Lederman and Cobbold are completely silent as to the administration of an APC. Beschorner does not administer the APC to an activated T cell. Eynon does not rely on an APC to induce tolerance, and is presenting the antigen to a naïve T cell, *i.e.*, unactivated T cell.

Step (b)- co-administration of an anti-gp39 antibody which binds to mouse or human gp39 on the activated T cell

The second step of the method- the administration of an anti-gp39 antibody- is also not taught or suggested by any of the cited references. All of the secondary references are silent as to the administration of an anti-gp39 antibody. The Examiner argues that "the teachings of Lederman et al. clearly provides for anti-CD40L (anti-5c8, anti-gp39, anti-CD40 ligand) antibodies to inhibit the immune response in order to treat disease conditions, such as autoimmunity." See Office Action dated June 14, 2006, page 5. However, the Lederman teachings do not teach a person of skill in the art to treat an autoimmune disease because the model systems used in Lederman are flawed. There are no data anywhere in Lederman showing the effect of monoclonal antibody 5c8 on autoimmune responses or autoimmune diseases. Also, there are no data showing the effect of normal human T cells expressing what is called T-BAM on an antigen-specific immune response *in vitro* or *in vivo*.

Lederman does not teach anything about the treatment of autoimmune disease because Lederman uses a human T cell line, Jurkat, which proliferates continuously in culture. One of skill in the art would not have used Jurkat T cells to study the role of monoclonal antibody 5c8 on autoimmune responses or autoimmune diseases because Jurkat is a transformed T cell leukemia line and cannot be used to induce antigen-specific responses *in vitro* or *in vivo*. At the time of the present application, one of skill in the art would have recognized that signaling a human T cell line, Jurkat, with an anti-CD3 monoclonal antibody, was not the same as signaling with an antigen.

Lederman simply used the Jurkat cells as a convenient means to study B cell activation. This is not the same as addressing the role of CD40-CD40L in autoimmune responses. Furthermore, it was known at the time of the invention that resting T cells do not express CD40L and that the expression of CD40L is regulated on T cells. Thus, the Jurkat cell subline (D1.1) used in Lederman, which is a continuously dividing T cell line and unlike normal T cells, constitutively expresses high levels of CD40L, to activate B cells, was not a good model for the interactions that could occur between normal T cells and normal B cells.

In the experiments where normal T cells are used in Lederman, a tumor promoting agent, PMA, and PHA, (Lederman, Example 6, col. 23, ll. 38-53), a combination of phorbol dibutyrate (PDB) and anti-CD3 (Lederman, Example 7, col. 23, l. 55- col. 24, l. 26)[1], or pokeweed mitogen (PWM) (Lederman, Example 7, col. 24, ll. 27-59) is used to activate the T cells. Lederman does not demonstrate that CD40L is induced on normal T cells under normal physiologic conditions.

Lederman does not provide evidence showing that the 5c8 anti-CD40L monoclonal antibody binds to cells other than human T cells stimulated with non-physiologic stimuli and the Jurkat human T cell line, and certainly provides no evidence that the 5c8 antibody can affect an autoimmune disease in an animal including humans. There are no functional data in Lederman using T cells activated with physiologic stimuli, and no data assessing the role of an anti-CD40L antibody *in vivo* which would be essential to know if the antibody could inhibit autoimmune disease.

Lederman as a primary reference does not teach the use of an anti-gp39 antibody to treat autoimmune disease. The secondary references are silent as to the use of an anti-gp39 antibody, thus, this limitation of the claimed method is not taught or suggested by any of the cited references, alone or in combination.

In summary, neither of the claimed limitations of the present invention are taught or suggested by the prior art references cited by the Examiner, either alone or in combination. For at

[1] In this experiment, the T cells were killed by fixation prior to being put in contact with the B cells.

least this reason, claims 82-94 are not obvious over Lederman in view of Beschorner, Cobbold, and Eynon.

(2) The Examiner has failed to cite references or general knowledge that would suggest or motivate one having ordinary skill in the art to modify or combine the reference teachings to arrive at the invention claimed in claims 82-94

The correct standard for combining prior art references requires that each reference must provide some suggestion or motivation to combine those features identified by the Examiner to arrive at the claimed invention (see MPEP § 2143). Here the Examiner states that "there is insufficient discouragement nor skepticism" regarding his combination of Lederman with Beschorner, Cobbold or Eynon. See Office Action dated June 14, 2006, page 6. Not only is this an incorrect statement, it shows he is clearly applying the wrong standard for a finding of obviousness based on the combination of cited prior art.

35 U.S.C. § 103 *requires assessment of the invention as a whole* such that the Examiner must show that an artisan of ordinary skill in the art at the time of invention, confronted by the same problems as the inventor and with no knowledge of the claimed invention, would have selected the various elements from the prior art and combined them in the claimed manner. *Princeton Biochemicals, Inc. v. Beckman Coulter, Inc.*, 411 F.3d 1332, 1337 (Fed. Cir. 2005); *Ruiz v. A.B. Chance Co.*, 357 F.3d 1270, 1275 (Fed. Cir. 2004); *Ecolochem, Inc. v. Southern Cal. Edison Co.*, 227 F.3d 1361, 1375 (Fed. Cir. 2000). Further, *references must be considered for all that they teach*, and may not be applied out of their own context to render a claimed invention obvious *absent any suggestion to do so. Ecolochem*, 227 F.3d at 1375. That is, "the 'as a whole' instruction . . . prevents evaluation of the invention part by part." *Ruiz*, 357 F.3d at 1275.

"The suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness." *In re Rouffet*, 149 F.3d 1350, 1357-58 (Fed. Cir. 1998). An Examiner may not use the claimed invention as an instruction manual or "template" to piece together the teachings of the prior art so that the claimed invention is rendered obvious. *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 546 (Fed. Cir. 1998) ("Determination of

obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention."); *Sensonics, Inc. v. Aeronsonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996) ("To draw on hindsight knowledge of the patented invention, when the prior art does not contain or suggest that knowledge, is to use the invention as a template for its own reconstruction--an illogical and inappropriate process by which to determine patentability."); *In re Oetiker*, 977 F.2d 1443, 1447 (Fed. Cir. 1992) ("The combination of elements from non-analogous sources, in a manner that reconstructs the applicant's invention only with the benefit of hindsight, is insufficient to present a prima facie case of obviousness."); *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992) (citing *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988)); *In re Gorman*, 933 F.2d 982, 987 (Fed. Cir. 1991) ("It is impermissible, however, to simply engage in a hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps."). That is, one cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. *In re Fritch*, 972 F.2d at 1266. Allowing the Examiner to use "the invention as a roadmap to find its prior art components, would discount the value of combining various existing features or principles in a new way to achieve a new result--often the very definition of invention." *Ruiz*, 357 F.3d at 1275.

In finding a suggestion or motivation to combine these references, the Examiner argues that the references do not teach away from the present invention and are properly combined because they are all directed to alternative tolerance induction regimens (Office Action dated June 14, 2006, page 6). In making this statement, the Examiner is over-generalizing the teachings of the references, taking the teachings out of context, and not considering the references for all that they teach. *Ecolochem*, 227 F.3d at 1375.

Beschorner discloses administration of APCs in an environment devoid of activated T cells and the Applicants' invention requires the administration of the APCs in an environment containing activated T cells. In fact, the presently claimed method of reducing T cell responsiveness relies upon blocking the interaction of the gp39 ligand with the gp39 expressed on the activated T cells. Therefore, a skilled worker would not have been motivated to combine the

teachings of Beschorner with the teachings of Lederman because the skilled worker would recognize that an anti-gp39 antibody can only bind to activated T cells expressing gp39, not unactivated T cells.

Furthermore, a skilled worker would also recognize that contact with an APC is necessary in order for T cells to become activated in the thymus, and that by administering an immunosuppressant, Beschorner teaches the depletion of endogenous APCs in the thymus, and thus, the depletion of mature, activated T cells, and any T cell pre-cursors.

Therefore, Beschorner teaches away from the presently claimed invention, which depends upon blocking the interaction of an activated T cell with an antigen, and one of skill in the art would not have been motivated to combine the teachings of the two references because "the line of development flowing from the reference's disclosure [Beschorner] is unlikely to productive of the result sought by the applicant." *Tec Air, Inc v. Denso Mfg. Mich., Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1991) (citing *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)). Beschorner teaches an opposite concept from the present invention, thus, teaching away from the presently claimed invention. Beschorner cannot be properly combined with Lederman to make an obviousness rejection. *In re Lundsford*, 148 U.S.P.Q. 721, 726 (C.C.P.A. 1966).

A skilled worker would also not have been motivated to combine the teachings of Cobbold with the teachings of Lederman because the antibody taught by Lederman, anti-CD40, and the antibody taught by Cobbold, anti-CD4, block T and B cell interactions with different mechanisms. The Lederman reference teaches that Lederman's antibody blocks CD40L in the "effector" phase (T cell induced differentiation of B cells into Ig-secreting cells), whereas Cobbold's antibody blocks CD4 in the "inductive" phase (initial physical interaction of a T cell with a B cell), which is prior to the effector phase (Lederman, col. 1, ll. 28-42). The induction phase requires CD4 and is inhibited by anti-CD4 antibodies. In contrast, the effector phase does not require CD4 and is not inhibited by anti-CD4 antibodies (Lederman, col. 1, ll. 43-51). Since Cobbold's method is already blocking the "inductive" phase and is useless in blocking the

"effector" phase, one of skill in the art would not have been motivated to look to Cobbold's teachings, or combine them with those of Lederman, to block the "effector" phase.

Finally, a skilled worker would not have been motivated to combine the teachings of Eynon with the teachings of Lederman because the skilled worker would recognize that only activated, not resting T cells, express gp39, and Eynon describes the use of resting T cells. Without the T cell expressing gp39, there would be no need to administer an antibody that recognizes and binds to gp39, as is done in Lederman.

In fact, Eynon's method of self-tolerance is hypothesized to be due the lack of co-stimulation or engagement of gp39 as shown:

> As outlined above, the interaction of antigen-specific resting T cell with an antigen-specific resting B cell may be ineffective [at activating a B cell to produce antibodies] due to lack of co-stimulator signal or signals ...
>
> Eynon, p. 132, col. 1, end of ¶ 1.

Although this sentence refers to prior work done using antigen-specific B cells as APCs, this mechanism was the basis for Eynon's study, since Eynon's method also depends on the use of unactivated B cells presenting an antigen to unactivated T cells (Eynon, page 132, col. 1, second ¶). This makes perfect sense given the fact that resting T cells lack gp39, and the ability to become "co-stimulated" and in turn, activate B cells.

The Examiner contends that Eynon provides sufficient motivation and expectation to achieve the present invention because "Enyon [sic] et al. teach that B cell presentation of antigen in the absence of appropriate help leads to specific antigen-specific T cell anergy in vivo." See Office Action dated June 14, 2006, page 3. Eynon does teach that B cell presentation of an antigen can lead to T cell anergy, however contrary to the presently claimed method, *Eynon is not teaching the blocking of the co-stimulatory or helper signal, but rather the use of T cell that never expressed the*

signal, i.e., a resting T cell. This disclosure, either alone or in combination with Lederman, would not lead to the presently claimed invention.

Thus, since Eynon's method does not involve an activated T cell, its teachings are opposite of Lederman, and the two references cannot be properly combined.

In view of the above, there would have been no motivation to combine Lederman with any of the secondary references, and for at least these reasons, the obviousness rejection of claims 82-94 should be withdrawn.

(3) The Examiner has failed to cite references that give rise to a reasonable expectation of success in achieving the invention defined in claims 82-94

The Examiner has presented references that upon combination with each other and/or the common knowledge of the art at the time of the invention would provide no reasonable expectation of success in achieving the invention claimed in claims 82-94. *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) ("both the suggestion and the expectation of success must be founded in the prior art, not the applicant's disclosure.")

For one reason, none of the references alone or in combination, disclose a method for inducing T cell tolerance by administering **both** an APC that presents an autoantigen to an activated T cell expressing mouse or human gp39 **and** an anti-gp39 antibody. As fully shown in Section I(A)(1), Lederman, the primary reference, does not disclose or suggest the administration of APCs that present an autoantigen to an activated T cell. The secondary references do not provide this missing limitation in that Beschorner and Eynon disclose the administration of APCs in an environment of unactivated T cells, and Cobbold is silent as to the administration of exogenous APCs.

Additionally, the references do not teach or suggest, either alone or in combination, the claim limitation of step (b): the co-administration of an anti-gp39 antibody. As shown in Section I(A)(1), the primary reference (Lederman) does not teach a person of skill in the art to use an

antibody to treat autoimmune diseases, and the secondary references are silent as to the administration of an anti-gp39 antibody.

More importantly combining the teachings from any of the three secondary references with Lederman would not achieve the present invention (as defined by the claims on appeal) with any reasonable expectation of success. Beschorner teaches administration of an APC in an environment devoid of activated T cells. Using the method of Beschorner combined with the administration an anti-CD40 antibody disclosed in Lederman would not achieve a reduction in T cell responsiveness as with the method of the present claims because there would be no activated T cell expressing gp39 to which the antibody could bind and block the interaction of gp39 with the gp39 ligand. Thus, the combination of these two references provides no reasonable expectation of success in achieving the claimed method.

The combination of Lederman and Cobbold would also not provide a reasonable expectation of success in achieving the claimed method. Cobbold discloses only the co-administration of anti-CD4 and anti-CD8 antibodies to induce T cell tolerance and prevent skin graft rejections. Lederman discloses the administration of an anti-CD40 antibody, alone. There is no teaching in either reference suggesting of the co-administration of an APC with these antibodies, as called for in the method of the present claims.

Additionally, as discussed above, Lederman's method and Cobbold's method block interactions in two completely different phases of the immune response. Thus, even of the teachings of the two references were combined, there would be no reasonable likelihood of success in achieving in the invention of the present claims.

Lastly, the combination of Lederman and Eynon would not have a reasonable likelihood of success in leading a person of skill in the art to the presently claimed method. This is so because the T cells used in Eynon are not activated and do not express gp39. Thus, like Beschorner, combining the method of Eynon using endogenous APCs (in the form of small resting B cells) to process the antigen and present it to unactivated T cells, and the method of Lederman of

administering an anti-CD40 antibody, would not achieve the presently claimed method of inducing T cell responsiveness because there is no gp39 on an activated T cell to which the antibody can bind and block interaction of the gp39 with the gp39 ligand. In short, the combination of these two references provides no reasonable expectation of success in achieving the method called for in the present claims.

Thus, one of ordinary skill in the art at the time of the invention would not have had a reasonable expectation of success based upon any combination of the teachings in the cited prior art and/or their knowledge to create the method of reducing T cell responsiveness called for by the claims on appeal, *i.e.*, by coadministering an APC that presents an autoantigen to an activated T cell expressing mouse or human gp39 and an anti-gp39 antibody.

VIII. Conclusion

For the foregoing reasons the Examiner's rejection of the pending claims should be reversed.

Dated: February 26, 2007

Respectfully submitted,

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CLAIMS APPENDIX

1.-81. Canceled

82. (Rejected) A method for reducing antigen-specific T cell responsiveness *in vivo*, which method comprises administering to a subject in need of such treatment:

(a) an antigen-presenting cell that presents an autoantigen to an activated T cell expressing mouse or human gp39; and

(b) an anti-gp39 antibody which binds to mouse or human gp39 on the activated T cell,

wherein the anti-gp39 antibody is administered prior to, concurrent with, or subsequent to administration of the antigen-presenting cell in an amount effective to reduce T cell responsiveness to the antigen-presenting cell.

83. (Rejected) The method of claim 82, wherein the antigen-presenting cell is selected from the group consisting of B lymphocytes, monocytes, dendritic cells, Langerhans cells, keratinocytes, endothelial cells, astrocytes, fibroblasts and oligodendrocytes.

84. (Rejected) The method of claim 82, wherein the antigen-presenting cell is a B lymphocyte.

85. (Rejected) The method of claim 84, wherein the B lymphocyte is an activated B lymphocyte.

86. (Rejected) The method of claim 85, wherein the activated B lymphocyte is a splenic activated B lymphocyte.

87. (Rejected) The method of claim 82, wherein the antigen-presenting cell is a lymphoid cell.

88. (Rejected) The method of claim 82, wherein the antigen-presenting cell is a peripheral blood lymphocyte.

89. (Rejected) The method of claim 82, wherein the antigen-presenting cell is a bone marrow lymphocyte.

90. (Rejected) The method of claim 82, wherein the antigen-presenting cell is a Langerhans cell.

91. (Rejected) The method of claim 82, wherein the antigen-presenting cell is a dendritic cell.

92. (Rejected) The method of claim 82, wherein the anti-gp39 antibody is an anti-human anti-gp39 antibody.

93. (Rejected) The method of claim 92, wherein the anti-human anti-gp39 antibody is humanized.

94. (Rejected) The method of claim 92, wherein the anti-human anti-gp39 antibody is a chimeric anti-human anti-gp39 antibody containing human constant regions.

EVIDENCE APPENDIX

None

RELATED PROCEEDINGS APPENDIX

None